

REMARKS

Status of the Claims.

Claims 26-28, 37, and 61-63 are pending with entry of this amendment, claims 1-25, 29-36, 38-56, 57-60, being canceled and no claims being added herein. Claim 26 is amended herein. Support for this amendment is found, for example, at page 53, lines 3-6, and the like.

New Matter.

The Examiner alleged that the limitation of a method for detecting colorectal cancer claimed in claims 26-28, 37, and 61-63 has no clear support in the specification and claims as originally filed. Applicants note that the specification clearly teaches increased copy number of the amplicon at 20q13 in colorectal cancer, page 12, lines 26-27. Nevertheless, to expedite prosecution, claim 26 is amended herein to simply recite "breast cancer" thereby obviating this rejection.

35 U.S.C. §112, Second paragraph.

Claims 26-28, 37, and 61-63 were rejected under 35 U.S.C. §112, second paragraph, as allegedly omitting essential steps. In particular, the Examiner alleged that the claims failed to link the results from the determination of a gene copy number with the preamble in the claim.

Claim 26 is amended herein to recite ". . . , where an increased copy number of nucleic acid sequences at chromosomal region 20q13.2 indicates the presence of a breast cancer cell that is likely to progress to a more malignant phenotype" thereby obviating this rejection.

35 U.S.C. §112, First Paragraph - Written Description.

The Examiner rejected claims 26-28, 56, 61-63 under 35 U.S.C. §112, first paragraph, as allegedly not enabled because "the claims as written encompass a method for detecting the presence or absence of neoplastic cells using probes with unknown structure and length provided said probes share a fragment with SEQ ID NO:9 and are capable of hybridizing to SEQ ID NO:9 via said common fragment under the stringent conditions recited in claims 26." The Examiner further asserted that the specification and claims lack information of the structure and function of the probes used for the claimed method and thus allegedly does not meet the written description requirement.

The Court of Appeals of the Federal Circuit has recently held that written description requirement of 35 U.S.C. §112, first paragraph does not impose a per se rule that the specification must recite the nucleotide sequence of claimed DNA when that sequence is already known in the field. As stated by the Court:

The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh.

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The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution. Both Eshhar and Capon explain that this invention does not concern the discovery of gene function or structure, as in Lilly. The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes. [emphasis added] (*see, Capon v. Eshhar, Fed. Cir., No. 03-1480, 8/12/05*).

In the instant case, the Sequence of SEQ ID NO:9 is provided. The generation of probes specific to target sequences is routine to those of skill in the art. Indeed such probes can be generated *ad nauseum* using commercially available software tools known to those of skill in the art (*e.g.*, Oligodb available through PubMed, Sarani from Strand Genomics, Visual OMP from DNA software Ind., *etc.*). Thus, once a target nucleotide sequence is known probes that specifically hybridize to that sequence under stringent conditions are also *de facto* known to those of skill in the art. In view of *Capon v Eshhar*, the Examiner's insistence that Applicants provide a "representative number of species" is simply not in accordance with prevailing law.

Suitable probe sequences are readily provided by routine use of probe design software packages or even by visual inspection of the sequence (for example the complement of SEQ ID NO:9) would readily be recognized as a suitable probe.

One of ordinary skill in the art would readily appreciate that Applicants were in possession of a the genus of probes that specifically hybridize under stringent conditions to a target polynucleotide sequence consisting of the sequence of SEQ ID NO:9. Consequently, given the level of skill in the art, it is readily apparent that Applicants were in possession of the claimed invention.

Accordingly the claims meet the Written Description requirement as articulated in *Capon*, and the rejection of claims 26-28, 56, 61-63 on these grounds should be withdrawn.

35 U.S.C. §112, First Paragraph - Enablement.

Claims 26-28, 37, 56, and 61-63 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled because:

- 1) Applicants have allegedly failed to establish that ZABC-1 is amplified in the 20q13.2 amplicon;
- 2) Even if SEQ ID NO:9 is the same as ZNF217 one cannot predict that SEQ ID NO:9 has increased copy number in breast or colorectal cancer. The amplification of the 260 kb common region of 20q13.2 is not detected the by ZNF217 probe per se, but by the probe; and
- 3) One cannot predict that ZNF217 is amplified in breast cancer because "ZNF125 [ZNF217] mRNA is overexpressed in cells that have the amplification of the 260 kb region as well as in cells that do not have the amplification (*see*, Office Action, page 8, lines 1-6); and
- 4) The method has allegedly not been shown to be effective in "any sample".

1) ZABC-1 and ZNF217.

A BLAST search of SEQ ID NO:9 shows 100% sequence identify with the GenBank entry AF312915 (*see*, Exhibit A). GenBank entry AF312915 references Collins *et al.* (2001) *Genome Res.* 11 (6), 1034-1042 which identifies the sequence as ZNF217 (*see*, Exhibits C and D). Applicants have established at ZABC1 probes target ZNF217.

2) Increased copy number of SEQ ID NO:9 is clearly seen in breast cancer cells.

Contrary to the Examiner's assertion, the prevailing scientific literature clearly establishes that ZABC1 (ZNF217) is amplified in a number of cancers. For Example, Collins et al. (2001) *Genome Res.* 11 (6), 1034-1042 clearly shows that ZNF217 is amplified in breast cancers (*see, e.g., Figure 1*).

This reference and Collins *et al.* (1998) *Proc. Natl. Acad. Sci., U.S.A.*, 95(15): 8703-8708) (previously submitted) teach that ZNF217 overexpression is associated with poor prognosis and identifies ZNF217 as a putative oncogene. Moreover the references teach that ZNF217 is overexpressed in all cell lines and tumors in which it is amplified:

ZNF217 is centrally located in the 260-kb common region of amplification, transcribed in multiple normal tissues, and **overexpressed in all cell lines and tumors in which it is amplified and in two in which it is not.** ZNF217 is predicted to encode alternately spliced, Kruppel-like transcription factors of 1,062 and 1,108 aa, each having a DNA-binding domain (eight C2H2 zinc fingers) and a proline-rich transcription activation domain.

* * *

ZNF217 has several features that suggest it is an oncogene involved in breast cancer. First, it is located in a narrowly defined region of recurrent maximal amplification apparently devoid of other transcribed genes.

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Finally, ZNF217 was transcribed at high levels in 10 of 10 tumors and cell lines with 20q13.2 amplification and 2 without amplification (cell line 600MPE and primary tumor T4) and at low levels in 17 of 19 tumors and cell lines without amplification. Thus, although amplification appears to be the predominant mechanism leading to overexpression, transcript abundance also may be increased by other mechanisms as occur for established oncogenes such as *ERBB2*, *MYC*, and *NMYC*.

The fact that ZNF217 is overexpress in some cancer cell lines where it is not amplified does not negative the efficacy of ZNF217 copy number as a diagnostic/prognostic as recited in the pending claims. Again, the Examiner is reminded that the claims recite "copy number" not "overexpression" and **every cell line** in which ZNF217 copy number was elevated showed elevated ZNF217 expression level.

Thus, a ZNF217 **amplification** (increased copy number), is a clear and unambiguous marker that the subject cell is a cancer cell, indeed a cancer cell likely to progress to a more malignant phenotype.

4) Test sample.

The Examiner alleged that the claims lacked enablement of a method of detecting breast or colorectal cancer, using "any sample". To expedite prosecution, claim 26 is amended herein to recite: "... contacting a nucleic acid sample **from breast tissue cells**. . . " thereby obviating this rejection.

Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. **Should the Examiner seek to maintain the rejections, Applicants hereby expressly request, on the record, that the Examiner call Applicants to arrange a telephone interview with the Examiner and the Examiner's supervisor.**

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3513.

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Respectfully submitted,



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